KIDNEY DISEASE CLINICAL STUDIES INITIATIVE
FEBRUARY 4-5, 2003
HYATT REGENCY, BETHESDA, MARYLAND

FEBRUARY 4, 2003

WELCOME AND INTRODUCTION

Dr. Josephine Briggs, director of the Division of Kidney, Urologic, and Hematologic Diseases (KUH) at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), welcomed workshop participants. She announced that the name of the program and workshop had been changed by the Steering Committee (SC) to the Kidney Disease Clinical Studies Initiative. The new name would more appropriately reflect the tenor of the new research model being planned by the National Institutes of Health and the nephrology community.

"This is a new paradigm for thinking about clinical research," Dr. Briggs said. "We want to perform better clinical research through a more efficient process.

Dr. Briggs thanked workshop participants for taking time out from their very busy schedules to assist in developing the new research paradigm. She acknowledged that tough budgetary times might be ahead, but said that she remains optimistic and believes that even if the NIH budget should be tightened, cost-effective approaches to strengthening the NIDDK's kidney disease clinical trials portfolio could be developed.

"I remain very committed to the notion that nephrology needs to move forward as an evidence-based discipline," Dr. Briggs said. "The crux of an evidence base is observations grounded in true randomized controlled trials that guide clinical decision making." She went on to say that the broad charge to the group is "to discuss and advise us on ways to strengthen our overall evidence base."

Dr. Thomas Hostetter, KUH senior scientific advisor and former ASN president, said that the seeds for the Kidney Disease Clinical Studies Initiative were sown at an American Society of Nephrology meeting a year ago. From that meeting came the idea that clinical studies need to be enhanced and facilitated through the support of small-scale pilot and feasibility trials and high-quality observational studies.

Dr. Hostetter also noted that another outcome of the March meeting was the need for an inventory of past, present, and planned clinical trials. The renal community has not been aware of the range of studies that KUH has sponsored, he explained. "Given the right circumstances, the right access, the right procedures, the community needs to have access to these resources for planning future trials and observational studies." For this reason, Dr. Hostetter said, the meeting agenda was designed to review prior trials, ongoing trials, and upcoming trials for the purpose of planning new trials. He also announced that KUH has prepared a new initiative for providing funding that would support planning for pilot

and feasibility trials or epidemiology studies of the R21 or R33 type that would lead to high-quality grants.

PURPOSE

Steering Committee (SC) co-chair Dr. John Sedor reviewed the goals of the consortium, which are summarized as follows:

- Increase clinical knowledge about kidney disease
- Identify the databases and biosamples that are available
- Identify and eliminate barriers to datasets and develop methods to facilitate data sharing and data mining
- Recommend policies to govern access to datasets generated by future KUH-sponsored studies
- Encourage submission of ancillary projects that build on ongoing clinical trials and epidemiological studies
- Measure outcomes and success of the initiative and make recommendations for future directions

Dr. Sedor also noted that the new planning activities mechanism developed by KUH will fund pilot studies that will gather important information for use in investigator-initiated clinical trials and thereby, will encourage more of them.

Co-chair John Stokes summarized the discussions at the SC meeting held the previous evening. During the meeting, he said, the SC recognized that its mission had changed from building a clinical trials consortium to constructing a more efficient process that would lead to better clinical research. The new process includes a program announcement (PA) that will request goal- or hypothesis-driven proposals. The PA will be posted on the NIH Web site and proposals submitted in response to it will be evaluated by the SC, which will select a small number [five or six]. Those selected will be funded through supplements to existing grants. Funding would range from approximately $30,000 to $50,000.

KDCSI Subcommittee Reports

Chairs of KDCSI Subcommittees on Pediatrics, Chronic Kidney Disease (CKD)/Progression, End Stage Renal Disease (ESRD), and Acute Renal Failure (ARF) briefly presented reviews of past, current, and planned NIDDK clinical trials in those specific areas. Dr. Stokes then asked meeting participants to keep in mind two things when they reconvene for focus group sessions in the afternoon: (1) to list the priorities for their fields and (2) to define important available resources that would help address these

priorities. The SC, he said, believes that the best and most efficient results are going to come from information in databases and biological samples collected in past, present, and future clinical trials.

DESCRIPTION OF TRIALS INVENTORY

Dr. John Kusek, director of the NIDDK/KUH Clinical Trials Program, described the division's efforts to pull together an inventory of administrative and scientific information from NIDDK-supported clinical trials. The inventory in intended to foster use of data and biological samples collected in those studies and promote the conduct of ancillary studies.

The inventory, which is currently limited to NIDDK-sponsored studies, includes the following information:

- Investigator-initiated RO1 studies
- Cooperative agreements
- Contracts initiated by NIDDK
- Completed studies
- Ongoing studies
- Studies funded but not yet implemented
- RFAs for programs yet to be reviewed

The inventory categorizes 20 major trials. Other information in the compendium is policy on the

- Use of data (when to share, patient confidentiality, resources)
- Use of biological samples (quantity, prioritization of studies, patient confidentiality, sharing policies)
- Conduct of ancillary studies (access to patient population, collaboration of lead investigators, resources)

PANEL REVIEWS OF SELECTED TRIALS

A select number of trials included in the KUH clinical trials inventory were briefly presented. They are listed below along with their presenters:

- Chronic Renal Insufficiency Cohort (CRIC), Dr. Harvey Feldman
- Hemodialysis (HEMO) Study, Dr. Andrew Levy
- National Analgesic Nephropathy Study (NANS), Dr. William Henrich
- Dialysis Access Consortium (DAC), Dr. Bradley Dixon
- Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT), Dr. Andrew Bostom
- Renin-Angiotensin System Study (RASS) Blockade in Diabetes, Dr. Michael Mauer
- Diabetes Pilot and Feasibility Study: Spironolactone, Dr. Robert Toto
- Diabetes Pilot and Feasibility Trial: COX 2 Inhibition, Dr. Julia Lewis
- Acute Renal Failure (ARF) VA/NIH, Dr. Paul Palevsky

[Editor's Note: The above trials are described in the KDCSI Inventory]

ACCESS TO DATA AND SAMPLES

Drs. Raymond Townsend, Lawrence Appel, Barry Freedman, and Rebekah Rasooly, respectively, discussed the availability of data sets and samples in four NIDDK studies: the Chronic Renal Insufficiency Cohort (CRIC), the African American Intervention Study of Kidney Diseases and Hypertension (AASK), the Family Investigation of Nephropathy of Diabetes (FIND), and the NIDDK Repository. Summaries of the discussions are as follows:

- The CRIC study is collecting demographic information for ancillary studies on all factors that might contribute to chronic renal insufficiency progression. This information will be stored in central location and will be available for additional, funded, hypothesis-driven studies (e.g., depression, nutrition, urinary minerals, analgesics, risk factor control, genes, lipids, sleep disorders, obstructive sleep apnea, vitamin D, echo and imaging data, and others). The study has three sources of ancillary study proposals: core CRIC centers, the science data support center, and external investigator applications.
- AASK, a clinical trial of 1,094 African Americans with hypertensive kidney disease, began in 1995 in 21 clinical centers. Study participants were randomized to one of two blood pressure goals and one of three initial hypertension therapies. The trial ended in September 2001. A five-year cohort study began in April 2002 with 675 of the original participants who are not on dialysis. "In the process, we collected a ton of data, including biological specimens," Dr. Appel said.

"Beginning with enrollment, we stored blood and urine… which was collected every six months thereafter." He said the repository was also enhanced by collection of fingernail clippings for heavy metal analyses and by plasma samples. AASK investigators are considering collecting these samples twice a year for the duration of the study for use in ancillary studies. Policy on use of samples gives priority to the study investigators, but outside investigators can submit proposals for use of the samples.

- FIND is a study that is searching for the genes responsible for diabetic kidney disease. The study has recruited 9,000 study participants (5,500 in the family-based study and 3,500 in the novel mapping by admixture linkage disequilibrium [MALD] study). According to Dr. Freedman, FIND was built with sharing data and samples in mind and "its biosamples could be used in perpetuity." Studies of non-diabetic nephropathy were also built into FIND.

- The NIDDK Repository is a central repository for samples collected from large studies. The samples will be useful to new studies. The repository has three components: a biosample repository; a database repository; and a genetics repository for the creation and maintenance of immortalized cell lines and DNA. The repository is slated to be operational in the fall of 2003. According to Dr. Rasooly, investigators who use the samples must be independently funded for ancillary and secondary studies.

WORKING WITH INDUSTRY

Dr. Edmund Lewis discussed his experience working with industry in the Collaborative Study Group, which was started in 1979. "One way or another, industry has to be involved," Dr. Lewis said. "Progress, that is drugs, is initiated by industry." The Collaborative Study Group undertook the captopril interventional trial for diabetic nephropathy. Half of the funds for the trial came from industry and half from NIH. A trial, he said, is important in terms of the biological phenomena and whether the trial can be sold to industry.

A summary of Dr. Lewis's observations and advice follows:

- Corporate growth involves voracious mergers and acquisition of entities with different cultures and priorities. For example, the captopril trial started with one company, which was then acquired by another; the first company was interested in diabetic nephropathy, the second wasn't.

- Corporate interests are generally dependent on financial gain. This implies the need for patent protection and FDA approval. Consequently, there are important problems that industry won't undertake.
- The company will consider how long they may have a patent. A pilot trial may not be attractive or may involve a soft endpoint. A large clinical trial may be impossible in some areas.

- IND requirement involves extensive documentation; this includes FDA approval of manufacturing techniques and facilities. A foreign company with a promising drug may deem a renal indication of low or no priority.

- Cardiovascular goals may trump a renal indication. Risk factors such as high cholesterol and hypertension may have much bigger markets.

- Best practice recommendations of institutional review boards may undermine the ability to do a renal study.

- Biotechnology companies, especially the small ones, are looking for a "hit" so that a larger company will buy them out. They use comprehensive research organizations (CROs) to recruit patients for the study, but CROs have no experience with renal studies. They come in with many promises but the chances for an investigator to have a role in decision-making are low.

Dr. Lewis concluded that complete independence from the pharmaceutical industry is possible, but the odds are against it. Cooperation between NIH and industry will allow more flexibility in the construction of trials.

RE-ENGINEERING THE CLINICAL RESEARCH ENTERPRISE

Dr. Robert Star, senior scientific advisor to DKUH, reported on the NIH Roadmap Initiative that was inspired by NIH Director, Elias Zerhouni, M.D., soon after he became director last spring. According to Dr. Star, Dr. Zerhouni's observations were as follows:

- Clinical research has evolved haphazardly. It started as a cottage industry at select centers. Now, it has become more complex, requiring regulation, technology, speed, and efficiency.

- The clinical research community needs a revolutionary transformation, a paradigm shift, to move into the 21st century. First, new researchers need individual apprenticeship to learn the discipline of clinical research. Second, in addition to a focus on mentoring, NIH must develop coaching for multidisciplinary teams. Third, rules and infrastructure need to be harmonized.

- Scientists must consider the next steps that will address these issues.

Last summer, NIH scientists as well as scientists from outside the NIH community were organized into roadmap groups that were asked to identify the most important issues facing medical research today, including the most promising opportunities, information gaps, and critical roadblocks to progress in biomedical research. Three broad themes emerged from the roadmap meetings:

- New pathways to discovery

- Multidisciplinary research teams of the future
- Re-engineering the clinical research enterprise

Over the next three to five years, the NIH Roadmap Initiative will rethink the technical and human infrastructure requirements for a more effective clinical research enterprise. The re-engineering effort will involve other government agencies, academic centers, community-based professionals, industry, and patient groups. The goal of the initiative will be to develop a more standardized and systematic national clinical research infrastructure with interoperable information systems. Dr. Star noted that this will include "an inventory of things that already exist, simplification of complex regulatory systems, and the creation of a [centralized] repository."

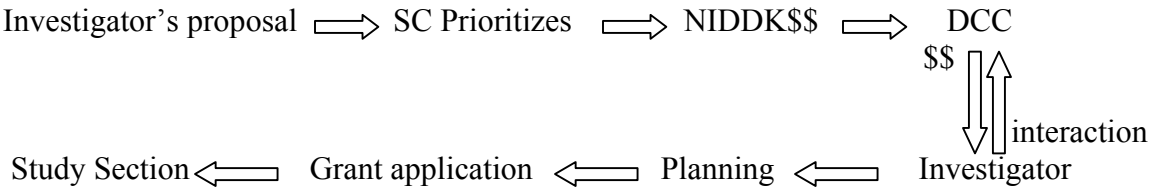
The following are a few of the many suggestions that have come from roadmap groups:

- Harmonize complex regulatory systems
- Develop standard nomenclature, data standards, and core data
- Develop interoperable networks with common infrasructures
- Certify the workforce
- Develop standards and training that lead to "safe haven"

The NIH Roadmap Initiative is an ongoing process, and Dr. Zerhouni will be seeking further input from the research community as well as from the public.

FUNDING MECHANISMS

Dr. Hostetter briefly spoke about the new funding mechanism for planning pilot and feasibility studies and epidemiology studies. Investigators will submit to Dr. Hostetter proposals that are three-pages or less, consisting of background, proposed aims and design, needs for planning the application, list of investigators and minimal references, and a percentage of effort among planning investigators and a data-coordinating center for statistical, design, and data analysis support. The Kidney Disease Clinical Studies Initiative Steering Committee will review the proposals and give them priority scores.



The first receipt date for planning support proposals is May 1, 2003; the second receipt date is July 1, 2003. R03 grants are an additional mechanism for planning support, but they are independent of the above process.

Dr. Catherine Meyers, director of the KUH Inflammatory Kidney Diseases Program, discussed the different types of R mechanisms available for funding studies (see table below). She also provided a draft of a standing program announcement (PA) that will encourage development of innovative and high impact pilot and feasibility studies and epidemiology studies as well as clinical trials. Grants available to investigators for these studies include the NIH Exploratory/Development Research Grant (R21), the Exploratory/Development Research Grant Phase 2 (R33), and the Phased Innovation Award (R21/R33 combined).

Table—R Mechanisms for Kidney Clinical Studies Initiative

Type	$ Max (direct)	Time	Review
R01—general	$ 500K	5 years	Center for Scientific Review (except if approved)
R21—pilot & feasibility	$ 275K	2 years	NIDDK Study Section
R33—trial implement	$ 500K	5 years	NIDDK Study Section
R03—planning/concept development	$ 50K	2 years	NIDDK Study Section

Dr. Briggs emphasized that review of grant applications is performed by administrative structures within the NIH that are separate from program management staff. “Review can be carried out in two different places, the Center for Scientific Review (CSR) or the review branches within the institute….” Dr. Briggs said. “The big advantage we feel of having planning support applications reviewed within the institute is partly dependent on a grant stream that will allow us to have review sections that deal with six or seven clinical grants at a time.” Dr. Briggs added that when grant applications go to CSR, they have generally been placed together in review categories where they are compared with very different kinds of work. “By creating this program announcement and an understanding with the institute [NIDDK], we are creating a setting in which these grants will be compared with other clinical investigative proposals,” she said.

Dr. Briggs also stated that the PA for R21 and R33 grants described by Dr. Meyers could be used for planning meetings and developing concepts for consortia. She added that the PA is a standing PA that is open for submissions at every grant cycle.

Dr. Kusek discussed how the new concept development mechanism will enhance ancillary studies. Although the funding is yet to be decided, KUH is working on developing a PA for planning ancillary studies to ongoing or already completed clinical trials and epidemiological studies. The PA is intended to stimulate not only investigators

who are participating in the conduct of an NIDDK-supported clinical trial and epidemiological study, but also outside investigators. Because of the paucity of past and current epidemiological studies, the PA will primarily focus on randomized clinical trials. Different avenues for investigators to pursue, Dr. Kusek noted, include new analyses of already completed studies or data sets that are already locked down, particular assays of archived specimens from completed trials or ongoing studies, new data collection in an ongoing study, new collection of biological samples in an ongoing study, and possibly meta analyses and analyses of large public-use databases such as NHANES.

FEBRUARY 5, 2003

SUBCOMMITTEE MEETINGS AND REPORTS

Subcommittees on Pediatrics, ARF, CKD/Progression, ESRD, and Glomerular Disease met in the afternoon to elucidate the important questions and issues that the Steering Committee of the KDCSI needs to consider when they evaluate various proposals and initiatives.

Subcommittee on Chronic Kidney Disease (CKD)/Progression
Dr. Harvey Feldman, presenter

The Subcommittee on CKD/Progression began their discussions thinking about large-scale clinical trials that would be the outcome of the development pathway that begins with planning activities. Dr. Feldman said that much of the discussion also centered on the importance of perfecting the ability of NIH-funded investigators and the NIH itself to interact with the private sector, recognizing that "we will have to rely more and more on these public-private partnerships."

Process Issues

- Develop guidelines regarding private/public partnership to encourage industry collaboration
- Encourage NIH to develop enhanced capability to interact with potential private sector partnerships (e.g., NIH could develop an office to facilitate this interaction)
- Clarify whether proposals are to be submitted directly to the Steering Committee and then triaged to data-coordinating centers (DCCs)
- Develop a spectrum of planning process activities:
    - Require no data from extant DCCs
    - Require data files for DCCs
    - Require data files and other analytic support
- Enhance access to information about NIDDK studies
    - Establish a Web-based inventory
    - Encourage public access to full protocols and manuals of procedures
- Provide incentives for clinicians to enroll patients (i.e., develop different models of incentives for patients to join trials)

Data Resources

- NIDDK-sponsored studies
- Medicare data (5% sample)
- National Health and Nutrition Examination Survey (NHANES)
- NIH-supported trials supported by institutes other than NIDDK (e.g., large cardiovascular trials)
- Industry-supported trials
- Meta-analytic data files

Priority Areas

- Achieve balance with respect to
    - Drug and non-drug research
    - Risk factor and intervention studies
- Prevent kidney disease (e.g., develop control groups for comparison with existing cases of CKD in NIDDK studies)
    - In kidney donors
    - In patients with kidney transplants
- Characterize the relationship between blood pressure and progression of CKD and encourage research activities that would define the relationship between blood pressure and the occurrence and progression of CKD ("24-hour blood pressure, nocturnal blood pressures and the like are important areas of investigation.")
- Determine the biomarkers associated with progression of CKD (e.g., proteinuria)
- Add markers of CKD to active studies not specifically focused on kidney disease
- Study the burden of the morbidity associated with cardiovascular disease in patients who have early CKD (i.e., before they develop metabolic disturbances).
- Develop networks and consortia of investigators and potentially providers for the study of rare diseases and drugs (e.g., drugs off patent) that are not going to be ultimately studied by the pharmaceutical industry
- Gene banking
- Study the barriers to delivery of health services

In conclusion, Dr. Feldman said that members of his subcommittee applauded the new initiative and felt that it would jumpstart research in kidney disease. He said that the priority areas outlined by his group were broad, but this was a reflection of the tremendous need for research in this area.

Subcommittee on Pediatric Kidney Disease
Dr. Norman Siegel, presenter

Clinical Studies Initiatives in Pediatric Kidney Disease

Studies Derived from Previous or Existing Databases:

- North American Pediatric Renal Transplant Cooperative Study (NAPRTCS)
    - Focal segmental glomerulosclerosis (CSFSGS)

  - Renal transplant
  - Chronic renal insufficiency
  - Dialysis
- Hemolytic Renal Syndrome (Early diagnosis of infection caused by Shiga-toxin-like *E. coli* is important to prevent renal involvement.)

Studies Derived from Previous or Existing Databases:

- Autosomal recessive polycystic kidney disease (ARPKD)
- IgA Nephropathy—Southwest Pediatric Nephrology Group (has biosamples and registry data)
- National Institute of Child Health and Human Development (NICHD) Perinatal Network (According to Dr. Siegel, this database has considerable data on serum creatinine in kidney function. The data was collected as part of other studies such as administering surfactant to babies with respiratory distress syndrome and it has never been analyzed for the potential impact on the kidneys during neonatal injuries.)
- National Longitudinal Study of Adolescent Health (ADD Health)
  - Biosamples
  - Registry data
  - Potential for studying natural history of kidney disease in children

New Areas for Exploration

- Glomerulopathies (will require development of consortia)
  - Natural history
  - Trials
  - Outcomes
  - Biomarkers
- Urinary tract infections
  - Vesicoureteral reflux
  - Renal scarring plus or minus prophylactic treatment
- Hypertension
  - Standards (e.g., there is little or no information on ambulatory blood pressures, what size the cuff should be, etc.)
  - Consequences (e.g., influence of hypertension on cardiovascular system of young child)
- Prenatal and congenital renal disease
- Determinants and outcome of solitary kidneys
- ESRD/Transplantation
  - Cardiovascular disease
  - Bone disease
  - Neurocognitive function (new methods of PET scans and neuroimaging are needed)
- Dialysis
  - Adequacy
  - Site of care (Many children receive care in facilities that are not pediatric care facilities. The adequacy of care in these situations needs to be

assessed through epidemiological studies of current databases. These studies need preplanning.)
- Acute renal failure diagnosis and treatment
- Adolescents
  - Development/rehabilitation
  - Transition of care (define and develop)
  - Address issues of cardiovascular disease
  - Address issues of neurocognitive development to prevent non-adherence
- Syndrome X: obesity, hypertension, diabetes mellitus type II (which is now seen in children, ages 8-12 years, in larger numbers)
- Complementary and alternative medical therapies
- Quality-of-life issues
  - How families adapt
  - Adherence
  - Psychosocial adjustment ("a tremendous problem")
- Adherence/psychosocial adjustment

Creation of a Consortium or Registry
- Develop a Pediatric Clinical Studies Collaborative
- Enhance interactions with other collaborative study groups to provide continuity of observation/study (Dr. Siegel noted that several of the studies presented on the first day of the meeting, particularly the study of folic acid, could possibly have been adapted for children. "We have to think of the continuity of care and stop the concept that there is a break in care between the 18 year old and the 22 year old," he said.)

Translational Research Areas
- Genetic aberrations in renal biopsy material (Because much of the biopsy material in children is not contaminated by preexisting vascular disease and hypertension, meaningful information could be derived from it in terms of biomarkers to progression and response to therapy.)
- Genotype and phenotype relationship (particularly [important] with regard to the plethora of newly emerging tubular disorders from Bartter's syndrome to magnesium wasting syndromes)
- Biomarkers for disease, progression of disease, and failure to respond to treatment

Discussion
Several participants suggested that the best population for studying the development of cardiovascular disease in children with early kidney disease is children with autosomal dominant polycystic kidney disease.

Subcommittee on Glomerular Diseases
Dr. Edward Lewis, presenter

Research Needs

- Translation of
    - Animal models studies
    - Therapeutic approaches studies
    - NIH-supported studies
    - Biotechnology (pharmaceutical) studies (Need to find out what compounds they are developing that could conceivably interrupt or deter glomerular disease. A database and a way to interact with these industries is critically needed.)
- Patients for clinical trials (a collaborative effort that would identify groups of people or individuals who would be immediately available for either a pilot study or a larger clinical interventional trial)
- Identification of a database that has information necessary for glomerular disease research and that could be used to derive meaningful questions for clinical trials (e.g., the European studies of vasculitis, in which information from databases turned out valuable studies)
- Standardization of definitions (could be done with pilot grants)

Priorities

- Genetics
- Biomarker development
- Effectiveness of current treatments
- Development of a paradigm for glomerular disease

The subcommittee selected refractory lupus nephritis as a starting point for a paradigm of glomerular disease because a pilot study would produce information that would lead to an interventional trial. The subcommittee suggested looking at a list of agents and prioritizing them in terms of potential for treatment, then testing them on a small group of patients—non-responders to standard treatment, for example. The results of the pilot study could be presented to industry scientists, not marketing people, with an idea for a large clinical trial.

NIH Studies

- Genotype/phenotype
- Collect material for further study
- Concept development funds could be used for defining a viable group of lupus nephritis patients to study

Subcommittee on End Stage Renal Disease (ESRD)
Dr. Glenn Chertow, presenter

Priority Rankings for Active Initiatives

- Priority 1—Cardiovascular Disease
    - Antioxidants (Secondary Prevention with Antioxidants of Cardiovascular Disease in ESRD Study [SPACE])

    - Hypertension
    - Dyslipidemia
    - Anti-inflammatory agents (ASA)
    - Sudden death: potential for use of beta adrenergic blockers and other treatments
- Priority 2—General Care of ESRD
    - Hypertension
    - Glycemic control
    - Peripheral vascular disease: foot exam, revascularization
    - Screening strategies (cancer and other general medical issues of ESRD)
- Priority 3—Rehabilitation
    - Vocational
    - Physical activity
    - Depression, hostility, other emotional factors
- Priority 4—Dialysis
    - Primary disease epidemiology
    - Erythropoietin resistance—Vitamin C
    - Degree of phosphorus control
    - Frequency of visits
    - Dry weight targets
    - 4 versus 3.5 (*qod*) versus 3 days/week
    - Validation of Kidney Outcomes Quality Initiative (KDOQI) guidelines
- Priority 5—Transplantation
    - Death with a functional graft (42%)
    - General care
    - Medical strategies: effects of overall survival, toxicities of certain drugs
    - Overlap with cardiovascular disease population

Resources

- Databases
    - United States Renal Data System (USRDS)
    - United Network for Organ Sharing (UNOS)
    - Dialysis Outcomes and Practice Patterns Study (DOPPS)
    - Medicare 5%
    - Medicaid dual
    - Clinical Performance Measures (CPM)/USRDS
    - CRP
    - Cooperative Cardiovascular Project (CCP)
    - Veterans Administration (VA)
- Studies
    - Hemodialysis Study (HEMO)
    - Dialysis Access Consortium (DAC)
    - 4-D (4-dichlophenoxyacetic acid) Study
    - National Cooperative Dialysis Study (NCDS)
    - Collaborative Hypertext of Radiology (CHORUS)
    - Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)

  - Adequacy of Peritoneal Dialysis in Mexico Study (ADEMEX)
  - Canada-USA Peritoneal Dialysis Study Group (CANUSA)

Intermediate Outcomes
- Cardiovascular
- Hemoglobin

Payors
- Pharma
  - Small market
  - Rare for ESRD patients to be included
  - Some interventions would be counter to profit motives
  - Barriers to study design
- Chains
  - Barriers to study designs (e.g., paying for extra treatment in frequent dialysis trials)

Building Consortia—Needs
- Develop incentives for chains
- Provide a salary supplement for investigator and coordinator
- Build infrastructure
- Perform additional studies of ESRD-related rare diseases
  - Heparin-induced thrombocytopenia
  - Calciphylaxis

Discussion
The Subcommittee discussed the following:
- A need for institutional guidance such as a person at NIH who would examine studies outside NIH that would be useful for the potential paradigm change
- A need for basic scientists
- Studies of atherosclerosis are good for collecting information on kidney disease
- A need for better communication, which could be achieved through a national clinical resource system, Web-based resources, a password-protected Web site that would have forums and a GP server that allows ideas to flow back and forth quickly
- The need for consistent funding—when there are gaps in funding there is reduced participation

Subcommittee on Acute Renal Failure (ARF)
Dr. Bruce Molitoris, presenter

Research Priorities
- Determine natural history of ARF
- Obtain information about early disease and standardize the definitions of ARF (there are 30-40 in the literature)

- Determine associated risk factors
- Elucidate markers of severity that help with prognosis (a troponin equivalent)
- Define clinical endpoints—what is successful therapy
- Develop standard treatment for collection and storage of samples/data

Stratify Patients

- Stratify into high or low risk for preventive studies
- Stratify prognosis/outcomes for therapeutic studies
- Develop standardized inclusion/exclusion criteria

Existing Resources

- Databases
    - PICARD Study (Diuretics, Mortality, and Non-Recovery of Renal Function in Acute Renal Failure)
    - VA/NIH Cooperative Study
    - ANP Database
    - Fenoldopam Database for ARF and Contrast Nephropathy
    - European databases/expertise (European databases are worldwide and should be mined for information)
- Networks
    - PICARD Study Group
    - Veterans Administration/NIH Cooperative (20 VA sites and 7 NIH)
    - Independent networks

Barriers and Possible Solutions

Barriers	Solutions
Small heterogeneous patient population	No way to get around this
Lack of early access to patients and to rapid screening methods for diagnosis	Form alliances with ICU physicians rather than call them later and ask them for help
Lack of industry attraction and approach	Standardize approach and provide a network for studies
Need for multiple therapies	Interact with industry and FDA

GENERAL DISCUSSION

One participant suggested a consensus conference to develop a network and to standardize definitions. Participants discussed the problem of multiple definitions for ARF. Dr. Molitoris suggested that perhaps a spectrum of symptoms for mild, moderate and severe ARF needs to be developed as was done for sepsis, congestive heart failure, and chronic obstructive pulmonary disease. He also mentioned the need for a large network to minimize heterogeneity.

CONCLUSION

Concluding the workshop, Dr. Sedor noted that there were four common themes in the subcommittee reports:

- Public-private partnership with NIH facilitation
- Role of infrastructure
- Access to current and old data
- Facilitation of communication between investigators interested in different areas

According to Dr. Hostetter, an overview of the new system and how it will work (the workshop notebook, including inventory) will be posted on the NIDDK/KUH Website and participants will be notified by e-mail when it is up. Letters of intent are due April 15 and July 1. He expects five or six proposals will be selected and funded. He also called for participants to obtain a copy of the draft program announcement for research grants for clinical studies in kidney disease at the registration desk and to look for the final announcement on the NIDDK/KUH Web site.

Dr. Stokes told participants that the conference exceeded his expectations and that he hopes it will stimulate many good ideas. He emphasized that the Steering Committee will decide the merit of a proposal based on the investigator's substantive letter of intent. Letters of intent, Dr. Stokes reiterated, should be three (3) pages long and contain the following information:

- What you want to do
- Why you want to do it
- What your rationale is for it
- What resources you need
- What you expect to accomplish
- What kind of people you need
- How much effort is entailed
- How much time is entailed

The Steering Committee will develop a priority ranking of the letters of intent and link the proposal to an existing NIH application, but that investigators could help by having a particular study in mind. He asked participants for their patience because, although the Steering Committee wants to do as good a job as it can, "we are plowing new ground and there are bound to be mistakes."